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# Finding the Key to Dialysis Catheter Lock

In this issue of the *Journal*, Souweine and colleagues (pp. 1024–1032) report the results of a large, multicenter, randomized, double-blind, placebo-controlled trial evaluating the use of ethanol lock to prevent dialysis catheter-related infections (CRI) in intensive care unit (ICU) patients (1). CRI are a major source of morbidity and mortality (2), and substantial efforts have been devoted to the reduction of CRI, including the development of a central line intervention "bundle" that has been shown to decrease infection rates. Although a key component of the central line bundle is the removal of unnecessary lines, line removal is often not possible for patients with dialysis-requiring acute kidney injury (AKI). As a consequence, temporary (nontunneled) dialysis catheters may be indwelling for days to weeks. A prospective trial focused on temporary dialysis catheters found a bacteremia rate of 3.8 per 1,000 catheter-days, with other trials finding similar rates ranging from 3.9 to 9.7 per 1,000 catheter-days (3). In the PICARD (Program to Improve Care in Acute Renal Disease) study, a prospective cohort of patients with AKI hospitalized in the ICU, sepsis developed in 40% of patients after the diagnosis of AKI at a median of 5 days after AKI. The need for dialysis (and presumably a temporary dialysis catheter) was independently associated with the risk for sepsis (4).

For patients with dialysis-requiring AKI, what can be done to reduce the risk for dialysis CRI? Some have proposed that patients who are likely to have dialysis-requiring AKI for more than a week should undergo tunneled catheter placement (5). Compared with nontunneled catheters, tunneled catheters are associated with a decreased risk for CRI because there is not a direct track from the skin into the vessel (in particular, over time, as fibrosis develops around the cuff). However, the rate of infection with tunneled dialysis catheters is still significant, and it may not be feasible to place tunneled catheters in critically ill patients with AKI for a variety of reasons.

A major mechanism for the development of CRI is related to bacterial biofilms (6). Biofilms are structured groups of bacteria that adhere to surfaces and, over time, coat the inner surfaces of indwelling catheters. They are difficult to eradicate even with systemic antibiotic therapy, and removal of the catheter is frequently necessary (7). Therefore, a number of investigations have been directed toward prevention of biofilm formation through use of antibiotic/antiseptic-impregnated catheters and antimicrobial and nonantimicrobial solution catheter locks. The catheter lock solution is a solution that sits in the catheter between dialysis sessions; typically, this solution contains an anticoagulant (heparin or citrate) to preserve catheter patency. A metaanalysis of 16 randomized controlled trials assessing antimicrobial catheter lock solutions for prevention of CRI in patients undergoing hemodialysis found decreased rates of CRI with antibiotic-containing catheter lock solutions compared with heparin lock (8). More recently, Moore and colleagues compared heparin with a gentamicin/trisodium citrate catheter lock solution in a prospective multicenter, observational cohort of patients receiving chronic dialysis dialyzing through a tunneled catheter and found that the gentamicin/citrate lock was associated with reductions in both catheter-related bloodstream infections (CRBSI) and mortality (9). However, current guidelines do not recommend routine use of antibiotic lock therapy for prevention of CRI because of concern for risks of emergence of resistant organisms, as well as adverse effects, toxicity, and allergic reactions to the antibiotic lock (2). This may be a particular concern in the ICU, where patients are already at high risk for infection with resistant organisms.

Ethanol is a safe, inexpensive agent that has been shown *in vitro* to eradicate bacteria and fungi from biofilms with a relatively short (1–2 min) treatment time (10). Furthermore, the use of ethanol should not be associated with the selection of more-resistant organisms. Souweine and colleagues evaluated the efficacy of a 2-minute ethanol lock to prevent CRI in 1,460 adult ICU patients who were undergoing insertion of a nontunneled dialysis catheter for dialysis, plasma exchange, or both (1). Patients who were anticipated to need a catheter for at least 48 hours were randomly

assigned 1:1 to receive a 2-minute catheter lock with either 60% w/w ethanol solution or 0.9% saline solution. Nonantimicrobial impregnated double lumen temporary dialysis catheters were placed under maximal barrier conditions, and catheters were maintained with a heparin-based lock solution after the ethanol/saline treatment. All catheters were evaluated for colonization at the time of catheter removal or ICU discharge. CRI was defined as both CRBSI and catheter-related clinical sepsis with negative cultures, which was defined by specific clinical criteria: body temperature 38.5°C or higher or 36.5°C or lower, catheter colonization, pus at the insertion site or resolution of fever or hypothermia within 24 hours after catheter removal and before any change in antimicrobial therapy, and absence of infection at other sites.

Overall, 1.6% of subjects in the control group and 2.3% of subjects in the ethanol lock group experienced CRI, with an incidence rate of 2.4 and 3.8 events per 1,000 catheter-days. These differences were not significant, nor was there a difference in the rate of catheter colonization (12.1 and 15.2 events per 1,000 catheter-days; $P = 0.57$). If anything, there was a trend toward harm with ethanol lock, with an increased incidence of catheter-related clinical sepsis (0.5 and 1.8 events per 1,000 catheter-days; $P = 0.03$). Of note, the study was powered to detect a 66% reduction in the rate of CRI with ethanol lock, with an anticipated event rate of 4% in the control group, and the sample size was increased from 1,300 to 1,490 at the first interim analysis because of the greater than anticipated number of catheters that remained *in situ* for less than 48 hours.

Strengths of the study include its large, multicenter design, rigorous study protocol with protocol-specified analyses of catheter colonization, and blinded adjudication of clinical events when catheter cultures were not available. Of catheters removed in the ICU, more than 90% of catheters were cultured, highlighting excellent compliance with the study protocol. Furthermore, the very low rates of CRI suggest outstanding compliance with established interventions to reduce the risk of CRI, but also limit the power of the study. Nonetheless, there was no trend in the study toward benefit with ethanol lock, and if anything, a suggestion toward harm, so the negative findings of this study are not a result of a lack of power. Limitations of this study include the dwell time of the ethanol lock and the limited prior data in support of this approach. For example, although Qu and colleagues demonstrated bacterial death in biofilm within 1 minute of exposure to 60–80% ethanol, with lower concentrations of ethanol (20–40%), much longer exposures (1–4 h) were required (10). Furthermore, all previous clinical trials used a longer duration of ethanol locks. The most comparable duration of time was a 15-minute dwell used in a randomized, double-blind placebo-controlled clinical trial of adult hematology patients, which did not show any significant reduction in CRBSI (11).

How does this study fit in the context of other studies of catheter lock solutions designed to reduce the risk for infection? We believe that the findings are quite consistent with the results of studies with citrate catheter locks. Freysz and colleagues compared sodium citrate with saline catheter lock solutions for nontunneled CVC in critically ill adults in a prospective randomized controlled trial. Although there was no difference in incidence of CRBSI, the citrate lock group had double the catheter life span (median, 12 vs. 6 d; $P = 0.0019$), as well as lower rates of catheter malfunction compared with the saline group (12). More recently, a metaanalysis of 13 randomized controlled trials comparing citrate and heparin locks in hemodialysis central venous catheters found that heparin and citrate locks were associated with similar rates of CRBSI; however, citrate plus an additional antimicrobial additive (e.g., gentamicin or taurolidine) was superior to heparin in the prevention of CRBSI. There was no significant difference between the preservation of catheter patency with the use of citrate versus heparin locks (13).

In sum, this rigorously executed, large, randomized clinical trial of ethanol lock of temporary dialysis catheters failed to suggest any benefit of ethanol lock, and supports other studies suggesting that catheter lock solutions that do not contain antimicrobials can improve catheter patency, and therefore function, but are not associated with decreased risk for CRI. ■

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# Nighttime in the Intensive Care Unit
## A Lens into the Value of Critical Care Delivery

Improving the value of critical care delivery requires efforts to augment the delivery of high-value services, such as having pharmacists on rounds (1) and regularly employing lung-protective ventilation. Improving value also requires reductions in the delivery of low-value care, as has been advocated by the Choosing Wisely campaign, including in the critical care context (2). On this front, a growing number of studies of what happens to patients in the intensive care unit (ICU) at night, a time when less resource-intensive care paradigms are often employed, are teaching us a great deal.

Recent examinations of nighttime in the ICU have called into question several processes and structures of critical care that seem valuable on their face. The first myth to be debunked by such studies is the view that because exposure to trained intensivists is associated with improved outcomes for patients in the ICU, a greater "dose" of exposure to such physicians is better still (3, 4). This position seems far less tenable after two multicenter observational studies (5, 6) and one single-center randomized trial (7) showed that in ICUs using high-intensity staffing during the day, there is no benefit to maintaining such staffing through the night. These and other findings have helped shape a more plausible alternate hypothesis that for the vast majority of patients in the ICU, it is sufficient to receive care in ICUs that employ multidisciplinary teamwork, protocol adherence, and subspecialty critical care training of daytime physicians.

The second premise to be questioned by research on the nocturnal goings-on in ICUs is that there are unambiguous virtues to maintaining continuity of physician coverage for seriously ill inpatients. In a study published in the *Journal* last year (8), Amaral and colleagues presented surprising data that nocturnal cross coverage by critical care fellows was actually associated with improved survival. Although it would be premature to advocate increased fragmentation of care on the basis of this report, the study casts important doubt on traditional assumptions that continuity is essential to high-value care delivery (9).

Finally, the notions that transitions into and out of the ICU at night pose independent threats to patients have long attracted interest and investigation. Many studies have suggested that patients discharged from ICUs at night have worse risk-adjusted outcomes (10, 11). As a consequence, avoiding nighttime discharges is increasingly viewed as a potential quality measure and has recently been used as an endpoint in rigorous ICU studies (12). However, limitations to prior studies preclude clear conclusions that nighttime discharges represent a practice to be avoided.

For example, a recent study (13) showed that prior reports (11) of an association between nighttime ICU discharge and increased risk for ICU readmission were likely biased by defining readmissions using a fixed time interval. Although the recent study confirmed that patients discharged from the ICU at night were indeed more likely to be readmitted within 48 hours, this increased risk vanished when readmissions were defined as occurring within 2 calendar days (13). Thus, prior associations between nighttime discharge and readmission were almost certainly attributable to the idiosyncrasies of patient flow, rather than to ICU error. Specifically, because most ICU admissions occur during late afternoon and evening hours, measuring readmissions in 24-hour increments increases the opportunities for readmission after nighttime, rather than morning or early afternoon, discharges, leading to spurious conclusions (13).

However, this phenomenon does not explain prior reports that patients discharged from the ICU at night have greater risks of subsequently dying in the hospital at any time. In the current issue of the *Journal*, Santamaria and colleagues (pp. 1033–1039) address this issue by examining ICU discharges among survivors of critical illness from 40 ICUs in Australia and New Zealand (14). Because these authors collected data prospectively for this study, they were able to adjust for patient characteristics at the time of ICU discharge, whereas earlier studies could merely adjust for acuity near the time of ICU admission (10, 11).

The authors found that compared with daytime ICU discharges, patients discharged at night were sicker, were more likely to have limitations on life support, and experienced higher crude rates of subsequent hospital mortality, despite no differences in subsequent care on the ward. However, after adjustment for available patient characteristics at the time of discharge, there ceased to be evidence of a heightened mortality risk among nighttime discharges. Further, in contrast to a prior study from the United Kingdom (10), patients discharged "prematurely" in the views of the ICU physicians did not experience increased mortality risk.

In interpreting these central findings, it is important to note that none of the 40 ICUs in this sample employed nighttime intensivists, tele-ICU, or coordination of discharges by nighttime nurse supervisors. This bolsters confidence that a truly heightened risk-adjusted mortality risk among nighttime discharges was not missed simply because these ICUs employed other resource-intensive nighttime models of care that might not be found elsewhere. A second strength is that the authors used state-of-the-art approaches to regression model building and testing.

Third, the authors conducted a potentially important secondary analysis using the hour at which patients were deemed ready for discharge as the exposure variable, rather than the actual discharge hour. Here, the authors found that even patients who were

ORIGINAL ARTICLE

# Ethanol Lock and Risk of Hemodialysis Catheter Infection in Critically Ill Patients

## A Randomized Controlled Trial

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## Abstract

**Rationale:** Ethanol rapidly eradicated experimental biofilm. Clinical studies of ethanol lock to prevent catheter-related infections (CRIs) suggest preventive efficacy. No such studies have been done in intensive care units (ICU).

**Objectives:** To determine whether ethanol lock decreases the risk of major CRI in patients with short-term dialysis catheters (DCs).

**Methods:** A randomized, double-blind, placebo-controlled trial was performed in 16 ICUs in seven university hospitals and one general hospital in France between June 2009 and December 2011. Adults with insertion of a nontunneled, nonantimicrobial-impregnated double-lumen DC for an expected duration greater than 48 hours, to perform renal-replacement therapy or plasma exchange, were randomly allocated (1:1) to receive a 2-minute catheter lock with either 60% wt/wt ethanol solution (ethanol group) or 0.9% saline solution (control group) at the end of DC insertion and after each renal-replacement therapy or plasma exchange session. The main outcome was major CRI defined as either catheter-related clinical sepsis without bloodstream infection or catheter-related bloodstream infection during the ICU stay.

**Measurements and Main Results:** The intent-to-treat analysis included 1,460 patients (2,172 catheters, 12,944 catheter-days, and 8,442 study locks). Median DC duration was 4 days (interquartile range, 2–8) and was similar in both groups. Major CRI incidence did not differ between the ethanol and control groups (3.83 vs. 2.64 per 1,000 catheter-days, respectively; hazard ratio, 1.55; 95% confidence interval, 0.83–2.87; $P = 0.17$). No significant differences occurred for catheter colonization ($P = 0.57$) or catheter-related bloodstream infection ($P = 0.99$).

**Conclusions:** A 2-minute ethanol lock does not decrease the frequency of infection of DCs in ICU patients.

Clinical trial registered with www.clinicaltrials.gov (NCT 00875069).

**Keywords:** catheter-related infection; renal-replacement therapy; dialysis catheter; prevention; ethanol

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## At a Glance Commentary

**Scientific Knowledge on the Subject:** Guidelines do not recommend prophylactic antiinfectious lock for short-term catheters because the pathogenesis of short-term catheter infection is classically related to extraluminal colonization originating from the insertion site. However, very few studies have assessed the efficacy of the preventive lock strategy in critically ill patients.

**What This Study Adds to the Field:** This study is the largest prospective study on dialysis catheters in the intensive care unit setting and demonstrates that prophylactic ethanol lock fails to prevent catheter infection. Our results support the recommendation to refrain from antimicrobial locks for short-term catheters.

Patients in the intensive care unit (ICU) often require short-term central venous hemodialysis catheters for renal-replacement therapy (RRT) or plasma exchange (PE). Central venous catheters are associated with infectious complications that increase mortality and ICU stay length (1–3). One method used to prevent these complications is the antimicrobial lock, in which antimicrobials fill and dwell in the catheter lumens when the catheter is not being used. The lock solution contains high antimicrobial concentrations to overcome the relative resistance of sessile bacteria in the catheter biofilm. Studies show that antibiotic lock decreases the risk of long-term hemodialysis catheter infection (4–6) but, when used repeatedly, may promote the selection of resistant organisms (7, 8). In a recent systematic review, antimicrobial-containing citrate lock solutions but not citrate alone was reported to decrease the incidence of long-term catheter infections in patients on chronic dialysis (9).

Ethanol may hold promise as a lock solution, because it is inexpensive, universally available, and effective against a broad spectrum of bacteria and fungi (10). No evidence of acquired resistance after exposure to high-concentration ethanol has been reported (11). Ethanol lock (EL) produced promising results in a pilot study in patients on chronic dialysis (12). No studies of EL in ICU patients have been reported.

The objective of this randomized controlled trial was to assess EL efficacy in preventing major catheter-related infections (CRIs) in ICU patients requiring short-term dialysis catheters (DC). Some of the results of these studies have been previously reported in the form of an abstract (13).

## Methods

### Study Design

We conducted a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in France. The study protocol was approved by the Sud-Est 1 ethics committee, France. Written informed consent was obtained from the patients or next of kin before inclusion.

### Participants

Eligible patients were adults (>18 yr) who required insertion of a nontunneled, nonantimicrobial-impregnated double-lumen DC with an expected duration of use longer than 48 hours. Exclusion criteria were known ethanol intolerance and pregnancy. The patients were enrolled in 16 ICUs in seven university hospitals and one general hospital.

### Interventions

Patients were randomly assigned in a 1:1 ratio to either a 60% wt/wt EL or a 0.9% saline lock (control). A 60% wt/wt EL solution corresponds to a greater than 75% vol/vol ethanol concentration, based on the accepted ethanol density of about 0.789.

All DCs in a given patient were managed as determined by the random allocation, until ICU discharge. The study lock was administered at the end of catheter insertion, after each intermittent hemodialysis/PE session, and at circuit termination for any reason in the event of continuous RRT. The nurse aspirated the study lock solution into a sterile syringe and injected 2 ml of the solution into each catheter lumen. The lock solution was left in the lumens for 2 minutes and then removed. Each lumen was then flushed with 20 ml of 0.9% saline and locked during the inter-RRT/PE periods with 0.9% saline containing 100 U/ml of unfractionated heparin; however, the attending physician could decide to refrain from using heparin in patients at high bleeding risk. During the inter-RRT/PE periods, neither the use of other lock solutions nor any manipulations of the catheter were allowed.

Maximal barrier precautions were followed for catheter placement and manipulation (*see* Table E1 in the online supplement). The choice of the catheter insertion site and decision to use ultrasound guidance for catheter insertion was at the discretion of the operator. Catheter insertion over a guidewire was allowed. The catheters were used only for RRT or PE. Alcoholic povidone-iodine solution or alcoholic chlorhexidine was used for skin antisepsis at catheter insertion and during dressing changes. Aromatic-polyurethane catheters were used in 15 centers and silicone catheters in one center, according to local standard practice.

Patients were followed up until death or 48 hours after ICU discharge. At catheter removal, catheter tips were cultured using a simplified quantitative broth dilution technique with vortexing in 11 ICUs and sonication in five ICUs. In patients who needed to keep the catheter after ICU discharge, paired blood samples were drawn simultaneously from the catheter hub and a peripheral vein before ICU discharge for determination of the differential time to positivity.

### Outcome Measures

The primary outcome measure was the number of major CRI episodes per catheter. Secondary outcome measures were the frequencies of catheter colonization, severe mechanical complications, and adverse events.

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Major CRI was defined as either catheter-related clinical sepsis without bloodstream infection (CRCS) or catheter-related bloodstream infection (CRBSI). CRCS was defined as presence of all four of the following criteria: body temperature greater than or equal to 38.5°C or less than or equal to 36.5°C, catheter colonization, pus at the insertion site or resolution of fever or hypothermia within 24 hours after catheter removal and before any change in antimicrobial therapy, and absence of infection at other sites.

CRBSI was the presence of all three of the following criteria: one or more positive peripheral blood cultures sampled immediately before or within 48 hours after catheter removal, quantitative catheter-tip culture positive for the same microorganisms or blood-culture differential time-to-positivity of 2 hours or more, and no other site of infection explaining the positive blood cultures (14). In patients with one or more blood cultures positive for coagulase-negative staphylococci, identity of pulse-field gel electrophoresis patterns in the catheter tip and blood cultures was required for a diagnosis of CRBSI.

For patients without catheter cultures, a masked adjudication committee determined whether major CRI was present. Sepsis or bloodstream infections were classified as catheter-related when there was no other detectable cause of sepsis with or without bloodstream infection.

Catheter colonization was a positive quantitative catheter-tip culture (cutoffs, 1,000 CFU/ml with vortexing [15] and 100 CFU/ml with sonication [16]). When the catheter was not removed, it was considered colonized when a blood culture from the catheter hub was positive.

Catheter dysfunction during RRT or PE sessions was defined as a problem with catheter flow, unfavorable inflow and outflow line pressures requiring catheter mobilization, inversion of lines, and flush through the catheter lumen. Severe mechanical complications consisted of catheter obstruction or dysfunction that persisted despite attempts to restore patency and required catheter removal, and of catheter damage, such as split or lumen rupture.

### Sample Size

We designed the study to detect a 66% decrease in the major CRI rate in the EL group (17), assuming a 4% rate in the control group. The statistical unit was the catheter. Based on previously published data, we assumed a mean number of 1.5 DCs per patient (18, 19). With a two-sided significance level of 5% and a power of 80%, and assuming two preplanned interim analyses on DC duration and adverse event rates after 400 and 800 inclusions, respectively, we needed to include 1,300 patients. However, the high proportion of patients with catheter duration use for less than 48 hours in the first interim analysis (>20% of catheters) led us to increase the total sample size to 1,490 patients. The decision to resize the sample size was not part of the original design. The rules governing the increase in sample size were defined at the time of the interim analysis.

### Randomization and Blinding

Randomization was done using a web-based random-number generator producing permuted blocks, with stratification on ICU.

The EL and 0.9% saline locks were identical in appearance. The solutions were colorless and provided in vials of identical shape and appearance. They were prepackaged centrally and then sent to each participating ICU. Each patient was assigned a number and received vials from the prepackaged box bearing that number. Concealment of allocation and provision of blinding was guaranteed by the French General Agency for Medicines and Health Products (AGEPS, AP-HP, Paris, France), which delivered patient-labeled vials containing either ethanol or 0.9% saline. All healthcare workers present in the room at the time of lock instillation from vial opening to vial discarding wore masks to block out odors. An audit to look for evidence of unblinding showed that none of the healthcare workers was able to unmask the study locks. In addition to the patients, physicians, and nurses, the outcome assessors and data analysts were masked to the treatment group until validation of the final results.

### Statistical Analysis

The primary outcome measure was analyzed in the intent-to-treat population. A predefined per-protocol analysis was performed in the population obtained by excluding patients with ICU stay lengths less than 48 hours, DCs that were inserted but not used, and DCs that were inserted and used but not locked with the study solution.

Predefined analyses of the primary outcome were performed in subgroups defined based on sex, insertion site, first inserted DC, type of RRT, and DC duration (≤5 vs. >5 d).

All comparisons of the two study groups were performed according to the statistical analysis plan. Only after full validation of all analyses were the statisticians and steering committee informed of group assignments. Infection incidence rates were computed as the number of catheters with infection (or colonization) divided by the number of catheter-days. Incidence rates are reported as the number of infections per 1,000 catheter-days.

Between-group differences in patient characteristics were tested using the chi-square test for qualitative variables and the Mann-Whitney test for quantitative variables. To assess between-group differences in catheter characteristics, we used the generalized estimating equation model, taking into account correlations between catheters in a given patient.

To take into account possible clustering caused by the presence of more than one catheter in some patients, we used a marginal Cox model for clustered data. This model both takes into account the censored nature of the data and accounts for intracluster (intrapatient) dependence (more than one catheter per patient) using a robust sandwich covariance estimate (PHREG in SAS, version 9.3; SAS Institute Inc., Cary, NC). Analyses were stratified by ICU. We checked the proportional hazards assumption and we looked for a qualitative interaction between treatment effects and centers. Statistical analysis was performed using SAS 9.3 (SAS Institute Inc.).

## Results

### Patient Population

The 16 ICUs participated in the study for a mean duration of 20 months (range, 2–31), during which 13,519 patients were admitted. Figure 1 is the flow chart for the ELVIS participants, who were enrolled between June 2009 and December 2011.

Table 1 lists the main characteristics of the 1,460 patients and Table 2 of the 2,172 catheters in the intent-to-treat population. These characteristics were not significantly different between the two groups. The per-protocol characteristics of patients and of

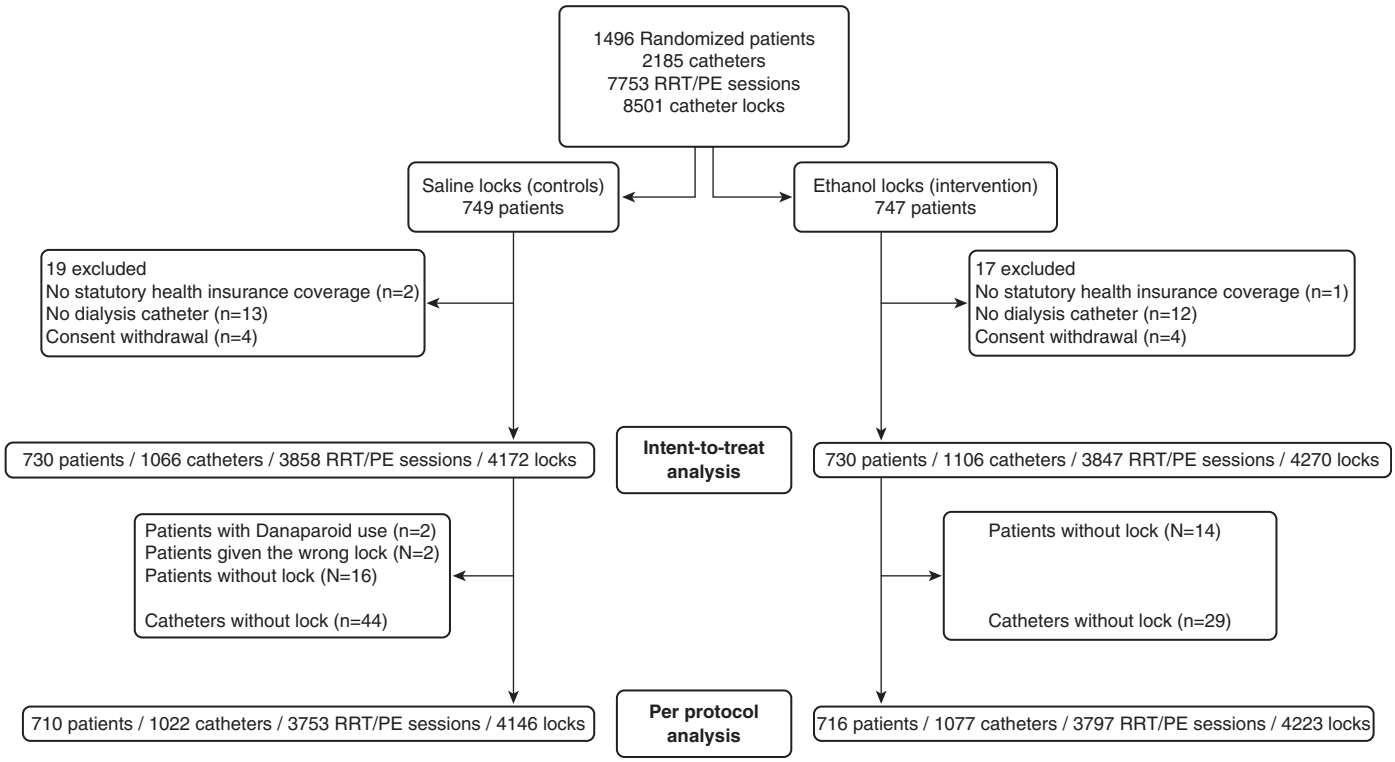


**Figure 1.** Flow chart for the ELVIS trial. PE = plasma exchange; RRT = renal-replacement therapy.

catheters are listed in the online supplement (*see* Tables E1 and E2).

### Infectious Complications

The final diagnoses at database lock were as follows: 42 (1.9%) catheters with major CRIs consisting of 27 CRBSIs and 15 CRCSs and 177 (8.1%) catheters with colonization. In the intent-to-treat population, the incidence rate of major CRI was not significantly different between the two groups (Table 3). The causative microorganisms are listed in the online supplement (*see* Table E3). Times to colonization, major CRI, and CRBSI showed no significant differences between the two groups (Figure 2). The per protocol analysis produced similar results (*see* Figure E1).

### Subgroup Analyses

The major CRI incidence rate was not significantly different between the two groups when we confined the analysis to males or females, to the first catheter inserted, to internal jugular and femoral catheters, to catheters used initially for intermittent hemodialysis, or to catheters used for continuous RRT (*see* Table E4). When we considered only the 965 catheters left in place for at least 5 days, the major CRI rate was 1.9% in the control group (nine events, 1.76 per 1,000 catheter-days) and 3.5% in the EL group (17 events, 3.32 per 1,000 catheter-days), yielding a slight nonsignificant trend toward a greater risk of major CRI in the EL group (hazard ratio, 2.2; 95% confidence interval [CI], 1.0–4.9; $P = 0.058$). In this subgroup, no such trend was detected between control and EL groups for catheter colonization (hazard ratio, 0.9; 95% CI, 0.6–1.3; $P = 0.50$) or CRBSI (hazard ratio, 1.01; 95% CI, 0.42–3.41; $P = 0.70$).

### Adverse Events

We found no significant differences between the control and EL groups for the proportion of sessions with catheter dysfunction (619 of 3,858 [16%] vs. 562 of 3,847 [14.6%], respectively; $P = 0.08$) or the proportion of catheters removed because of catheter dysfunction or obstruction (242 of 1,066 [22.7%] vs. 270 of 1,106 [24.4%], respectively; $P = 0.35$). There were no reports of catheter damage or clinical adverse events during study lock administration. When we compared silicone and aromatic polyurethane catheters, we found no significant difference in the proportion of RRT/PE sessions with catheter dysfunction (16.3 vs. 15.2%, respectively; $P = 0.60$) or in the proportion of catheters removed because of catheter dysfunction or obstruction (19.7 vs. 24.0%; $P = 0.21$), respectively.

## Discussion

In this large double-blind, randomized, placebo-controlled study of critically ill patients, a 2-minute EL applied to DCs after insertion and after each RRT or PE session or at the end of continuous RRT failed to prevent major CRI, CRBSI, or catheter colonization.

To our knowledge, four prospective randomized controlled trials have assessed the clinical impact of 70% vol/vol EL for preventing catheter infections (12, 20–22). Two trials used a double-blind design and included adult hematology patients with long-term tunneled catheters (20, 21). One of them included 60 patients with catheters in place for approximately 13 days and found that a daily lock with 70% ethanol and a 2-hour dwell time induced a fourfold

**Table 1.** Characteristics of the 1,460 Patients in the Intent-to-Treat Population

| Characteristic | All Patients (*n = 1,460*) | Control Arm (*n = 730*) | Ethanol Lock Arm (*n = 730*) |
|---|---|---|---|
| Age, yr, median (IQR) | 65 (56–75) | 66 (56–76) | 65 (56–75) |
| Male, n (%) | 890 (61) | 446 (61.1) | 444 (60.8) |
| BMI,* median (IQR) | 26.7 (23.2–31.2) | 27.1 (23.2–31.7) | 26.2 (23.1–30.5) |
| ⩾1 comorbidity, n (%) | 1,101 (75.4) | 549 (75.2) | 552 (75.6) |
| Immunocompromised, n (%) | 318 (21.8) | 145 (19.9) | 173 (23.7) |
| Hospital stay length at ICU admission | 1 (0–5) | 1 (0–5) | 0 (0–4) |
| SAPS II at ICU admission, median (IQR)† | 65 (50–81) | 65 (50–81) | 66 (51–82) |
| SAPS II at study inclusion, median (IQR)† | 68 (51–83) | 67 (51–82) | 68 (51–84) |
| SOFA at study inclusion, median (IQR)‡ | 12 (8–15) | 12 (8–15) | 12 (8–15) |
| Admission category, n (%) | | | |
| Medical | 1,280 (87.6) | 640 (87.7) | 639 (87.5) |
| Scheduled surgery | 68 (4.7) | 35 (4.8) | 33 (4.6) |
| Unscheduled surgery | 112 (7.7) | 54 (7.4) | 58 (8) |
| Main reason for ICU admission, n (%) | | | |
| Septic shock | 434 (29.8) | 214 (29.3) | 220 (30.1) |
| Other shock | 200 (13.7) | 98 (13.4) | 102 (14) |
| Acute respiratory failure | 281 (19.2) | 149 (20.4) | 132 (18.0) |
| Coma | 82 (5.6) | 45 (6.2) | 37 (5.1) |
| Acute renal failure | 314 (21.5) | 145 (19.9) | 169 (23.2) |
| Other reasons | 149 (10.2) | 79 (10.8) | 70 (9.6) |
| Mechanical ventilation at study inclusion, n (%) | 1,141 (78.2) | 577 (79) | 564 (77.3) |
| ICU stay length at inclusion, d, median (IQR) | 1 (0–2) | 1 (0–3) | 1 (0–2)§ |
| ICU stay length at first study catheter, d, median (IQR) | 2 (1–3) | 2 (1–4) | 2 (1–3)‖ |
| Catheters/patient, n (%) | | | |
| 1 | 1,065 (73) | 529 (72.5) | 536 (73.4) |
| 2 | 219 (15) | 119 (16.3) | 100 (13.7) |
| ⩾3 | 176 (12.1) | 82 (11.2) | 94 (12.9) |
| Type of session, n (%) | | | |
| No RRT/PE administered | 38 (2.6) | 16 (2.2) | 22 (3.0) |
| PE only | 36 (2.5) | 19 (2.6) | 17 (2.3) |
| RRT only | 1,056 (72.3) | 541 (74.1) | 515 (70.5) |
| Both RRT and PE | 330 (22.6) | 154 (21.1) | 176 (24.1) |
| No. of RRT/PE sessions, median (IQR) | 3 (1–7) | 3 (1–7) | 3 (1–6) |
| ICU stay length, d, median (IQR) | 11 (5–22) | 11 (5–22) | 10 (4–22) |
| Hospital stay length, median (IQR) | 25 (11–47) | 25 (12–47) | 25 (11–48) |
| ICU mortality, n (%) | 639 (43.8) | 325 (44.5) | 314 (43.0) |
| Hospital mortality, n (%) | 717 (49.1) | 364 (49.9) | 353 (48.4) |

*Definition of abbreviations*: BMI = body mass index in kg/m$^2$; ICU = intensive care unit; IQR = interquartile range; PE = plasma exchange; RRT = renal-replacement therapy; SAPS II = Simplified Acute Physiology Score II; SOFA = Sequential Organ Failure Assessment.
*214 missing data.
†The score can range from 0 to 162.
‡The score can range from 0 to 24.
§$P = 0.001$.
‖$P = 0.002$.

decrease in the CRBSI rate compared with heparinized saline (20). The other double-blind study included 376 patients with 448 catheters left in place for approximately 60 days and compared daily (or weekly in outpatient) 15-minute lock with ethanol or placebo for preventing endoluminal CRBSI (21). Although the results did not reach formal statistical significance, there was a trend toward efficacy (incidence rate ratio, 0.59; 95% CI, 0.27–1.30; $P = 0.19$) (21).

The third study was an open trial in 49 patients on chronic-dialysis with tunneled DCs maintained for very long times (>100 d) (12). EL instillation once a week for a 48-hour interdialytic period was associated with a nonsignificant 67% decrease in the CRBSI incidence rate compared with standard heparin locks three times a week. The prophylaxis EL strategy is designed to prevent endoluminal catheter infection, which is thought to predominate among long-term catheters. This may explain why these studies produced consistent results, although the EL dwell time varied from 15 minutes to 2 days. The fourth study was an open trial in patients with short-term central venous catheters after heart surgery. The study, initially planned for 950 patients, was prematurely stopped after enrollment of 200 patients (median catheter duration, 6 d) because of adverse events, despite a 60% lower CRBSI rate in the intervention group (2.1 vs. 5.2 per 1,000 d; $P = 0.33$) (22).

We found no effect of a 2-minute EL administered for a median of three times per catheter with median catheter use duration of 4 days. The characteristics of dialysis catheterization were consistent with those in other studies of short-term DCs in critically

**Table 2.** Characteristics of the 2,172 Catheters in the Intent-to-Treat Population

| Variable | All Catheters (*n* = 2,172) | Control (*n* = 1,066) | Ethanol Lock (*n* = 1,106) |
|---|---|---|---|
| Presence of another catheter at the time of insertion, n (%) | 1,901 (87.5) | 940 (88.2) | 961 (86.9) |
| Insertion site, n (%) | | | |
| Internal jugular | 663 (30.5) | 325 (30.5) | 338 (30.6) |
| Femoral vein | 1,486 (68.4) | 727 (68.2) | 759 (68.6) |
| Subclavian vein | 23 (1.1) | 14 (1.3) | 9 (0.8) |
| Right side | 1,295 (59.6) | 622 (58.3) | 673 (60.8) |
| Catheter exchange over a guidewire, n (%) | 274 (12.6) | 132 (12.4) | 142 (12.8) |
| Experience of the operator <50 procedures,* n (%) | 1,436 (66.7) | 706 (66.9) | 730 (66.6) |
| Alcohol-based skin antiseptic solution, n (%) | | | |
| 5% povidone-iodine, 70% ethanol | 836 (38.5) | 402 (37.7) | 434 (39.2) |
| 0.5% chlorhexidine, 67% ethanol | 1,298 (59.8) | 643 (60.3) | 655 (59.2) |
| 0.25% chlorhexidine, 0.025% benzalkonium chloride, 4% benzyl alcohol | 38 (1.7) | 21 (2) | 17 (1.5) |
| Systemic antimicrobials at catheter insertion, n (%) | 1,670 (76.9) | 823 (77.2) | 847 (76.6) |
| Catheter use, n (%) | | | |
| No RRT/PE performed | 86 (4.0) | 33 (3.1) | 53 (4.8) |
| PE only | 71 (3.3) | 32 (3.0) | 39 (3.5) |
| RRT only | 1,977 (91.0) | 985 (92.4) | 992 (89.7) |
| Both PE and RRT | 38 (1.7) | 16 (1.5) | 22 (2.0) |
| Number of RRT/PE sessions per catheter, median (IQR) | 2 (1–5) | 2 (1–5) | 2 (1–4) |
| At least one catheter dysfunction during RRT/PE sessions, n (%) | 682 (8.9) | 343 (8.9) | 339 (8.8) |
| Total number of catheter dysfunctions, n (%) | 1,181 (15.3) | 619 (16.0) | 562 (14.6) |
| Number of study locks per catheter, median (IQR) | 3 (2–5) | 3 (2–5) | 3 (2–5) |
| Number of study locks at catheter insertion, median (IQR) | 1 (0–1) | 1 (0–1) | 1 (0–1) |
| Catheter use duration, d, median (IQR) | 4.2 (2–8) | 4.3 (2–8) | 4.2 (2–8) |
| Catheter days, n | 13,037 | 6,496 | 6,541 |
| Inflammation at insertion site, n (%) | | | |
| Redness | 83 (3.8) | 33 (3.1) | 50 (4.5) |
| Purulent discharge | 13 (0.6) | 4 (0.4) | 9 (0.8) |
| Catheter left in place at ICU discharge, n (%) | 213 (9.8) | 106 (9.9) | 107 (9.7) |
| Catheter removed in the ICU, n (%) | 1,959 (90.2) | 960 (90.1) | 999 (90.3) |
| Reason for catheter removal, n (%)† | | | |
| Catheter no longer needed | 574 (29.3) | 285 (29.7) | 289 (28.9) |
| Catheter dysfunction | 512 (26.2) | 242 (25.2) | 270 (27.0) |
| Suspected catheter infection | 216 (11.0) | 102 (10.7) | 114 (11.4) |
| Death of the patient | 537 (27.4) | 272 (28.3) | 265 (26.6) |
| Other reasons | 120 (6.1) | 59 (6.1) | 61 (6.1) |
| Catheter tip culture performed at catheter removal, n (%)†‡ | 1,785 (91.1) | 872 (90.8) | 913 (91.4) |

*Definition of abbreviations*: ICU = intensive care unit; IQR = interquartile range; PE = plasma exchange; RRT = renal-replacement therapy.
*20 missing data (10 in each group).
†The denominator is the number of catheters removed in the ICU.
‡One missing datum.

ill patients (18, 19, 23–25). The low catheter colonization rate in the control arm compared with previous studies (24), which suggests advances in preventive measures over the last decade, may have limited the power of the study. However, there was no trend in the current study toward benefit with the ethanol intervention.

The rationale for using an EL dwell time of only 2 minutes was based on several factors. First, *in vitro* studies have demonstrated that short exposures to

**Table 3.** Incidence Rate of Catheter Colonization and Catheter-related Infections in the Ethanol Lock and Control Groups

| | Cumulative Incidence [*n* (%)] | | Incidence Rate per 1,000 Catheter-Days | | | |
|---|---|---|---|---|---|---|
| | Control | Ethanol Lock | Control | Ethanol Lock | HR (95% CI) | *P* Value |
| Major CRI | 17 (1.6) | 25 (2.3) | 2.64 | 3.83 | 1.55 (0.83–2.87) | 0.17 |
| CRCS | 3 (0.3) | 12 (1.1) | 0.47 | 1.8 | 3.71 (1.11–12.11) | 0.03 |
| CRBSI | 14 (1.3) | 13 (1.2) | 2.17 | 1.99 | 1.01 (0.45–2.23) | 0.99 |
| Colonized catheter | 78 (7.3) | 99 (9.0) | 12.08 | 15.18 | 1.10 (0.80–1.49) | 0.57 |

*Definition of abbreviations*: CI = confidence interval; CRBSI = catheter-related bloodstream infection; CRCS = catheter-related clinical sepsis without bloodstream infection; CRI = catheter-related infection; HR = hazard ratio.

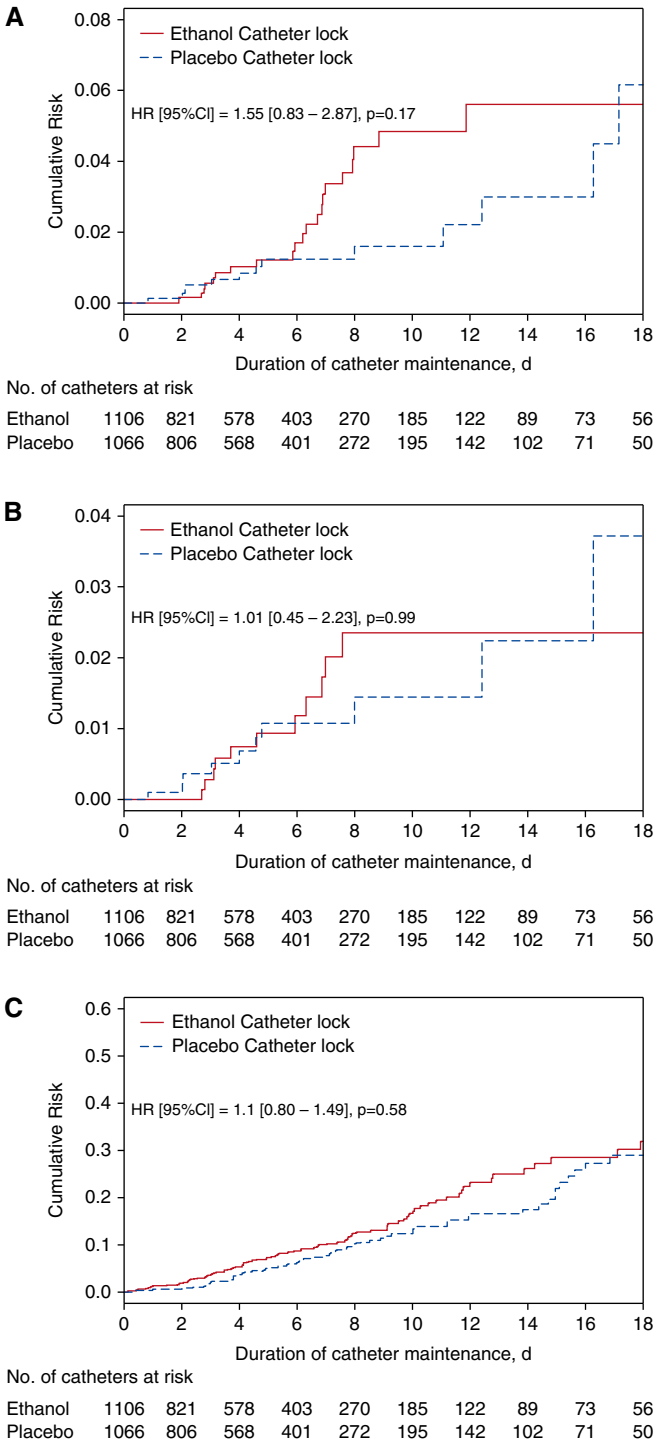


**Figure 2.** Overall Kaplan-Meier plots of time to events (intent-to-treat analysis). (*A*) Major catheter-related infections. (*B*) Catheter-related bloodstream infection. (*C*) Catheter colonization. CI = confidence interval; HR = hazard ratio.

high-concentration of ethanol are effective in reducing experimental biofilms (13, 26). In an *in vitro* study of nine coagulase-negative *Staphylococcus* isolates in biofilms developed on microplates, the biofilm cells of all isolates were killed within 1 minute of exposure to 60–80% ethanol (26). Similarly, another *in vitro* study used established biofilms on catheter segments and found that exposure to 60% wt/wt ethanol for only 2 minutes significantly decreased the *Staphylococcus aureus* and *Pseudomonas aeruginosa* biofilm loads and eradicated *Staphylococcus epidermidis*, *Klebsiella pneumonia*, and *Candida albicans* biofilms (13). The 1-cm catheter segments in the latter experiment were highly infected, with initial cell counts of $10^5$ to $10^6$, far higher than the cutoffs widely used to define catheter colonization in clinical settings ($10^3$ CFU/ml with vortexing and $10^2$ CFU/ml with sonication). However, the extent to which these experimental data on EL duration and concentration are relevant to clinical practice remains unclear.

Second, we limited the duration of catheter ethanol exposure to avoid ethanol-induced catheter damage (27–30). Consequently, we did not leave the EL in the lumens during the interdialytic period. Third, leaving the EL for a longer period would have interfered with standard clinical practice, generating additional openings and closings of the catheters and increasing the nurse workload.

Preventive locks combat only intraluminal organisms. Several studies in patients with end-stage renal disease suggest that antiseptic locks may prevent long-term DC infections (31, 32). Our working hypothesis involved a key contribution of intraluminal colonization to the development of major CRI, even with short-term catheters, because RRT requires frequent handling, connection, and disconnection of the hubs and circuits. However, in a *post hoc* analysis of the 121 colonized DCs (defined as a positive quantitative DC-tip culture) for which blood samples were obtained through the DC hub at the time of DC removal, we found that hub blood cultures yielded the microorganisms identified by vortexing/sonification in only 43 cases (36%). This finding suggests that extraluminal organisms were the source of colonization in most cases.

Two recent single-center studies including ICU patients suggest that interdialytic citrate lock may help to prevent DC infection (25) or colonization (33). The first was a small, open, randomized controlled study of 78 patients but showed CRBSI incidence rates 10 times higher than expected (25). The other retrospectively compared two historical cohorts matched on a propensity score and had a DC colonization rate in the control arm of 38.7 per 1,000 days, more than twofold that seen

in our study (33). The results of these studies may encourage physicians to adopt prophylactic locks for preventing DC infections in ICU patients. The negative results of our large study may prevent this change in practice and add important data for establishing further recommendations on this topic. Our results can probably be generalized to other antimicrobial locks, because ethanol is among the most potent antibiofilm biocides; and to other central venous catheters, in which colonization results mainly from biofilm formation on the external catheter surface (34). Thus, our results support the recommendation to refrain from antimicrobial locks for short-term catheters (35).

In our study, EL was removed from the catheter. As previously reported with this technique (12, 20), no clinical adverse events related to EL were recorded, in contrast to experience with EL locks flushed through the catheter (21, 22). EL did not result in catheter dysfunction or occlusion, in agreement with other reports (12). No catheter damage was observed, in keeping with experimental data showing that exposure of silicone and aromatic polyurethane catheters to 40–70% ethanol had only marginal effects on the mechanical and ultrastructural properties of the catheters (28, 29, 36).

The external validity of our findings deserves discussion. First, CRI without bacteremia may be difficult to diagnose. However, all episodes of suspected CRI or colonization were reviewed and classified by an adjudication committee whose members had no role in patient management and were masked to the study group. Furthermore, the results regarding CRI were similar to those for catheter colonization and CRBSI, whose definitions relied solely on objective criteria. Second, the duration of catheter use was short. Nevertheless, EL was not significantly effective in the subgroup of 943 catheters left in place for more than 5 days. Third, we did not study long-term catheters, such as those used by patients on chronic hemodialysis. The case mix and catheter maintenance duration in our study are consistent with earlier reports (18, 19, 24, 25, 37, 38), indicating that our population was representative of ICU patients requiring RRT.

In conclusion, this study shows that a 2-minute EL failed to reduce infection rate and was potentially harmful. ■

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